

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) A method for evaluating the potential of a chemical entity to bind to all or any part of Site II comprising:
 - (a) docking a chemical entity into all or any part of the cavity circumscribed by a Site II, wherein said Site II is a structure defined by structure coordinates that describe conserved residue backbone atoms having a root mean square deviation of not more than 2.0 Å from the conserved residue backbone atoms described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:13 according to Table I; and
 - (b) analyzing structural and chemical feature complementarity between said chemical entity and all or any part of said Site II.
2. (Original) The method of claim 1, wherein the Site II is an NHR Site II.
3. (Original) The method of claim 1, wherein the Site II is an SHR Site II.
4. (Original) The method of claim 1, wherein the Site II is a GR Site II.
5. (Currently Amended) A method of designing a ligand of Site II comprising:
 - (a) modeling all or any part of a Site II, wherein said Site II is a structure defined by structure coordinates that describe conserved residue backbone atoms having a root mean square deviation of not more than 2.0 Å from the conserved residue backbone atoms described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:13 according to Table I; and
 - (b) based on said modeling, designing a chemical entity that has structural and chemical feature complementarity with all or any part of said Site II.
6. (Currently Amended) A method for identifying a modulator of an NHR comprising:

- (a) docking a test molecule into all or any part of the cavity circumscribed by a Site II, wherein said Site II is a structure defined by structure coordinates that describe conserved residue backbone atoms having a root mean square deviation of not more than 2.0 Å from the conserved residue backbone atoms described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:13 according to Table I;
 - (b) analyzing structural and chemical feature complementarity between the test molecule and all or any part said Site II; and
 - (c) screening the test molecule in a biological assay of modulation of an NHR.
7. (Original) The method of claim 6 further comprising one or more of the following:
- (d) screening the test molecule in an assay that characterizes binding to a Site II; and
 - (e) screening the test molecule in an assay that characterizes binding to Site I.
8. (Original) The method of claim 6, wherein the modulator of an NHR induces transrepression.
9. (Original) The method of claim 6, wherein the modulator of an NHR is a dissociated compound.
10. (Original) The method of claim 6, wherein the modulator of an NHR antagonizes a modulator that induces transactivation.
11. (Original) The method of claim 9, wherein the dissociated compound is an SHR dissociated compound.
12. (Original) The method of claim 11, wherein the SHR dissociated compound is a GR dissociated compound.
13. (Original) The method of claim 6, wherein the Site II is an NHR Site II selected from the Site IIs of the group consisting of: RXR-alpha; RXR-beta; progesterone receptor (PR); androgen receptor (AR); estrogen receptor-alpha (ER-alpha); ER-beta; vitamin D receptor (VitDR); peroxisome proliferator activated receptor-gamma (PPAR-gamma); thyroid receptor-alpha (TR-alpha); TR-beta; mineralocorticoid receptor (MR); and glucocorticoid receptor (GR).

14. (Original) The method of claim 13, wherein the NHR Site II is an SHR Site II selected from the Site IIs of the group consisting of: PR; AR; ER-alpha; ER-beta; MR; and GR.
15. (Original) The method of claim 14, wherein said SHR Site II is a GR Site II.
16. (Original) The method of claim 15, wherein the GR Site II is selected from the Site IIs of the group consisting of: human GR; rat GR; mouse GR; sheep GR; marmoset GR; squirrel GR; pig GR; guinea pig GR; and m'az monkey GR.
17. (Currently Amended) The method of claim 13, wherein the NHR Site II is a RXR-alpha Site II composed of amino acids L236-P244, A272-A273, Q276-W283, G305-S313, H316-R317, A320-V321, T329, L368-G369, and R372 of SEQ ID NO:3 according to Figure 2.
18. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a RAR-gamma Site II composed of amino acids S194-P202, L233-A234, C237-F244, A266-R274, T277-R278, T280-E282, D290, T328-G329 and S332 of SEQ ID NO:4 according to Figure 2.
19. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a PR Site II composed of amino acids M692-V698, L721-G722, Q725-W732, S754-G762, W765-R766, K769-H770, P780, F818-L819 and K822 of SEQ ID NO:5 according to Figure 2.
20. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a AR Site II composed of amino acids E678-V684, L708-G709, Q712-W719, S741-A749, W752-R753, T756-N757, P767, F805-L806 and K809 of SEQ ID NO:6 according to Figure 2.
21. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a ER-alpha Site II composed of amino acids L320-I326, L348-A349, E352-W359, A381, W382-G389, W392-R393, E396, P405, F444-V445 and K448 of SEQ ID NO:7 according to Figure 2.
22. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a ER-beta Site II composed of amino acids L273-H279, L297-A298, E301-W308, C330-G338, W341-R342, D345, P354, Y393-L394 and K397 of SEQ ID NO:8 according to Figure 2.

23. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a VitDR Site II composed of amino acids L136-D144, L182-V183, S186-F193, S215-R223, E226-S227, T229-D231, G238, H279-V280 and M283 of SEQ ID NO:9 according to Figure 2.
24. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a PPAR-gamma Site II composed of amino acids Y219-P227, R288-S289, A292-Y299, G321-M329, S332-L333, N335-K336, E343, L384-A385 and I388 of SEQ ID NO:10 according to Figure 2.
25. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a MR Site II composed of amino acids E743-I749, L772-A773, Q776-W783, S805-A813, W816-R817, K820-H821, P831, Y869-T870 and K873 of SEQ ID NO:11 according to Figure 2.
26. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a TR-beta Site II composed of amino acids T226-Q235, I267-I268, A271-F278, C300-R308, V311-R312, D314-E316, G324, V362-A363 and Q366 of SEQ ID NO:12 according to Figure 2.
27. (Currently Amended) The method of claim 13, wherein the ~~the~~ NHR Site II is a GR Site II composed of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:13 according to Figure 2.
28. (Currently Amended) The method of claim 27, wherein the structure coordinates of the GR Site II define the structure of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:13 according to Table I, Table III, Table IV, or Table V.
29. (Currently Amended) A method for identifying a ligand of Site II comprising:
- (a) docking a test molecule into all or any part of the cavity circumscribed by a Site II, wherein said Site II is a structure defined by structure coordinates that describe conserved residue backbone atoms having a root mean square deviation of not more than 2.0 Å from the conserved residue backbone atoms described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:13 according to Table I;

- (b) analyzing structural and chemical feature complementarity between the test molecule and all or any part said Site II; and
 - (c) screening the test molecule in an assay that characterizes binding to a Site II.
30. (Original) A ligand of a Site II, wherein said Site II is a structure defined by structure coordinates that describe conserved residue backbone atoms having a root mean square deviation of not more than 2.0 Å from the conserved residue backbone atoms described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:13 according to Table I.
31. (Original) A modulator of an NHR, wherein said modulator has been identified by the method of claim 6.
32. (Original) A modulator of an NHR that is a ligand of claim 30.
33. (Original) A method of modulating an NHR comprising administering a modulator of an NHR in an amount sufficient to modulate the NHR, wherein said modulator of an NHR is a modulator of claim 31.
34. (Original) A method of modulating an NHR comprising administering a modulator of an NHR in an amount sufficient to modulate the NHR, wherein said modulator of an NHR is a modulator of claim 32.
35. (Original) A method of treating an NHR-associated disease comprising administering to a subject in need thereof, in an amount effective therefore, at least one modulator of an NHR of claim 31.
36. (Original) A method of treating an NHR-associated disease comprising administering to a subject in need thereof, in an amount effective therefore, at least one modulator of an NHR of claim 32.
37. (Original) A mutant NHR, or a mutant portion of an NHR, comprising one or more amino acid mutations in Site II.

38. (Original) A method of measuring the binding of a test molecule to Site II comprising:
- (a) incubating an NHR with a ligand of Site II and said test molecule; and
 - (b) measuring the ability of said test molecule to compete for binding to said Site II with said ligand, wherein said ability to compete is the measure of binding of said test molecule to Site II.
39. (Original) The method of claim 38, wherein step (a) further comprises a Site I ligand, wherein the ligand of Site II inhibits the binding of the Site I ligand to Site I, wherein the test molecule does not inhibit the binding of the Site I ligand to Site I, and wherein the measurement of the ability of said test molecule to compete for binding to said Site II is a measurement of the Site I ligand binding to Site I.